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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/506,942	02/18/2000	Jean-Marc Balloul	032751-027	9626

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BURNS DOANE SWECKER & MATHIS L L P
POST OFFICE BOX 1404
ALEXANDRIA, VA 22313-1404

EXAMINER	
FOLEY, SHANON A	

ART UNIT	PAPER NUMBER
1648	

DATE MAILED: 03/09/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/506,942	BALLOUL ET AL.	
	Examiner	Art Unit	
	Shanon Foley	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 December 2003*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *32,36,38,40,44,46-49,53-56,62,64,65,69,71,72,74,75,79 and 80* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *32,36,38,40,44,46-49,53-56,62,64,65,69,71,72,74,75,79 and 80* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☒ Certified copies of the priority documents have been received in Application No. 09/043933.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

In the paper submitted December 1, 2003, applicant amended claims 32, 38, 40, 44, 49, 65, 70, 74 and cancelled claims 50, 51, 57, 58, 76 and 77. Claims 32, 36, 38, 40, 44, 46-49, 53-56, 62, 64, 65, 69, 71, 72, 74, 75, 79 and 80 are pending and under consideration.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 40 and 49 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The claims state that E6 is a nononcogenic variant that is deleted of amino acids. It is not clear which amino acids are deleted. However, claim 75 states that the E6 amino acids that are deleted are 111-115, which is described in the specification on page 19, lines 3-8. In the interest of compact prosecution, it is presumed that the deleted amino acids in claims 40 and 49 are 111-115. This presumption does not relieve applicant of the burden of responding to this rejection.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 32, 36, 38, 53 and 54 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lowy et al. (US 5,618,536), Hagensee et al. (Journal of Virology. 1993; 67 (1): 315-322),

Borysiewicz et al. (Lancet. June, 1996; 347: 1523-1527), Galloway (Infectious Agents and Disease. 1994; 3: 187-193), and Meyer et al. (Journal of General Virology. 1991; 72: 1031-1038), as further evidenced by Boursnell et al. (US 5,719,054).

Applicant states that the amended claims require that the DNA sequences are under the control of individual expression elements. Applicant argues that Lowy et al. do not teach an anti-papillomavirus composition based on an MVA vector, but only teaches vaccinating with a protein-based composition. Applicant argues that the DNA molecule of Lowy et al. is used to direct the expression of VLPs and is not used as a therapeutic vehicle. Applicant asserts that Lowy et al. do not provide any experimental data supporting the therapeutic immunoprotection of the chimeric VLPs against HPV-induced tumors. Applicant further states that Lowy et al. do not demonstrate that conformational epitopes required for therapeutic CTL-mediated immunity are retained in the VLPs.

Applicant argues that Hagensee et al do not remedy the deficiencies of Lowy et al. Applicant specifically argues that the skilled artisan would not have been motivated to use the vaccinia virus of Hagensee et al. to avoid producing VLPs. Applicant further argues that Hagensee et al. do not teach expressing the early papillomavirus antigens for therapeutic benefit. Applicant asserts that even if the skilled artisan were motivated to use the vaccinia vector of Hagensee et al., the skilled artisan would have expressed polypeptides to produce chimeric VLPs by combining the teachings of Lowy et al. and Hagensee et al.

Applicant argues that Borysiewicz et al. does not suggest incorporating L1 and L2 into the vaccinia encoding the late papillomavirus polypeptides.

With respect to the teachings of Galloway, applicant argues that the reference does not teach a composition comprising an MVA vector co-expressing L1, L2, E6 and E7 polypeptides under independent expression control elements. Applicant asserts that the ordinary artisan would not have arrived at the instant invention because of Galloway's statement that it is unclear whether early and late polypeptide combinations could provide effective protection and treatment against HPV-induced disease. Applicant does not point to where this statement is though. Applicant briefly notes a clinical trial assay. However, reference of this assay is not of record and is not considered relevant to the instant rejection.

Regarding the teachings of Meyer et al. applicant asserts that the reference does not discuss HPV polypeptides. Applicant further argues that Meyer et al. do not teach that 4 or 5 different genes can be expressed in a single MVA vector and that the ordinary artisan would have no expectation of success for doing so. Applicant also asserts that co-expression of two genes can be problematic, but provides no evidence of this assertion.

In conclusion, applicant states that the references in combination do not provide motivation for one skilled in the art to use a single MVA vector to co-express papillomavirus genes under independent expression elements.

In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). Applicant discusses individual limitations not taught by the references. However, limitations not found in one prior art

reference are supplied by another reference. The combination of all the references as a whole teaches all of the limitations claimed.

In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992).

As applicant discusses on page 16 of the response, teachings of Lowy et al. demonstrate that late papillomavirus polypeptides, L1 and L2 induce prophylactic protection against papillomavirus infection. The last paragraph of the previous Office action on page 6 states that although Lowy et al. suggest incorporating papillomavirus E6 or E7 polypeptides into the composition and teach inducing neutralizing antibodies against E7 that is incorporated into an L1/L2 capsid, Lowy et al. does not expressly teach incorporating papillomavirus polypeptides into a vaccinia vector composition.

However, Hagensee et al. not only teach expressing L1 and L2 from a vaccinia vector, but also teach that L1 and L2 expressed from the vector are indistinguishable from HPV-1 virions from plantar warts. This intact conformational expression of the L1 and L2 from the vaccinia vector is essential because contrary to applicant's assertion, Lowy et al. teach that the presentation of conformational epitopes in L1 and L2 are required for the induction of immune reactivity, see column 3, lines 60-62 and column 6, lines 41-46. It is also noted that Hagensee et

al. expresses L1 and L2 from different promoters within the vector, see the first paragraph under the Materials and Methods" section on page 316 and Figure 1.

It is maintained that one skilled in the art at the time the invention was made would have been motivated to express and administer the papillomavirus polypeptides of Lowy et al. in the vaccinia vector comprising the 7.5K vaccinia promoter of Hagensee et al. to eliminate the time-consuming step of expressing and harvesting the recombinant polypeptides from cell culture. This motivation is established by knowledge generally available to one of ordinary skill in the art to reduce the number of steps required. In this case, Lowy et al. clearly teaches prophylactic efficacy of the papillomavirus late proteins and Hagensee et al. demonstrate that the late proteins expressed from a vaccinia vector possess the conformational epitopes required to induce a protective immune response, taught by Lowy et al. Therefore, the time required for one to purify the late proteins for prophylactic administration is unnecessary from the teachings of Hagensee et al.

Further, one of ordinary skill in the art at the time the invention was made would have had a reasonable expectation for expressing the polypeptides of Lowy et al. in the vaccinia vector of Hagensee et al. to elicit a protective immune response because Lowy et al. teach that presentation of conformational epitopes in L1/L2 is required for induction of immune reactivity, see column 3, lines 60-62 and column 6, lines 41-46, and Hagensee et al. teach that expression of L1 and L2 capsids from the vaccinia virus vector are indistinguishable from HPV-1 virions obtained from plantar warts, see the abstract, results and discussion sections. Therefore, the conformational epitopes required to be present in order to induce an immune response taught by

Lowy et al. are present in the polypeptides expressed by the vaccinia virus vector of Hagensee et al.

In the paragraph bridging page 7 of the previous Office action, it is stated that although Lowy et al. suggest incorporating papillomavirus E6 or E7 polypeptides into the composition and teach inducing neutralizing antibodies against E7 that is incorporated into an L1/L2 capsid, neither Lowy et al. nor Hagensee et al. expressly teach incorporating papillomavirus E6 and E7 polypeptides into a composition.

However, Borysiewicz et al. teaches a Wyeth strain vaccinia virus encoding papillomavirus polypeptides E6 and E7 under the control of the 7.5K promoter to treat cervical cancer, see the abstract and "Vaccination with TA-HPV and patient monitoring" section on page 1524. Although applicant argues that Borysiewicz et al. do not suggest incorporating L1 and L2 into the vaccinia vector, these limitations are specifically addressed by the teachings of Hagensee et al. and Lowey et al.

Further, Galloway teaches that the early proteins, E6 and E7, from the papillomavirus are therapeutic in nature while the late proteins, L1 and L2 are prophylactic, see the abstract and the paragraph bridging pages 190 and 191. The teachings of Galloway are based on a "Mini Review" of facts present in the prior art literature, not mere hypothesis, see the first line above the title of the reference. The conclusions of Galloway promoting a papillomavirus vaccine are based upon "the encouraging results with vaccines against animal PVs", see item (c) within the abstract. These results include protective efficacy demonstrated by several studies administering papillomavirus L1 and L2 polypeptides in various animal species, see the full paragraph in column 1 on page 190. The conclusions of Galloway concerning the therapeutic efficacy of

papillomavirus polypeptides E6 and E7 are also based upon several experiments demonstrating tumor regression in animal models, see the paragraph bridging pages 190-191.

The teachings Borysiewicz et al. and Galloway remedy the lack of therapeutic teachings regarding E6 and E7 of Lowey et al. and Hagensee et al.

It is maintained that one of skill in the art at the time of the invention would have been motivated to combine E6 and E7 of Borysiewicz et al. into the vaccinia vector of Hagensee et al. expressing the L1 and L2 proteins of Lowy et al. to treat and prevent papillomavirus infection in a host. One of skill in the art at the time of the invention would have had a reasonable expectation of success of producing the claimed invention because L1 and L2 possess prophylactic properties (discussed by Lowy et al. and Galloway) and E6 and E7 possess ameliorative properties (discussed by Borysiewicz et al. and Galloway).

Although Meyer et al. do not discuss papillomavirus polypeptides, Lowy et al., Hagensee et al., Borysiewicz et al. and Galloway do. Meyer et al. not only the vaccinia MVA strain, but also provides motivation to use it as an expression vector.

In response to the new limitation that the instant polypeptides be placed under the control of independent elements and applicant's assertion that the skilled artisan would not have a reasonable expectation of success for expressing different genes in the same vector, the teachings of Boursnell et al. provide evidence to the contrary. Boursnell et al. clearly demonstrate expressing 4 different papillomavirus genes from different promoters in a vaccinia vector, see Figure 26b, column 3, lines 29-35 and column 8, lines 24-37. Boursnell et al. clearly demonstrate that expression of multiple genes from different promoters is certainly possible in a vaccinia vector.

One of ordinary skill in the art at the time the invention was made would have been motivated to express the HPV polypeptides of Lowy et al., Hagensee et al., Borysiewicz et al. and Galloway in to the MVA vector of Meyer et al. under the control of different promoters, taught by Boursnell et al. to express the proteins from independent control elements in order to control transcription and subsequently, the amount of protein expressed in the cell. One of ordinary skill in the art at the time the invention was made would have had a reasonable expectation of producing the construct claimed because Boursnell et al. teach individual expression of different HPV polypeptides in a vaccinia vector and MVA of Meyer et al. is a vaccinia vector. Therefore, the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made, absent unexpected results to the contrary.

Claims 40, 57 and 58 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lowy et al. (US 5,618,536), Hagensee et al. (Journal of Virology. 1993; 67 (1): 315-322), Borysiewicz et al. (Lancet. June, 1996; 347: 1523-1527), Galloway (Infectious Agents and Disease. 1994; 3: 187-193), and Meyer et al. (Journal of General Virology. 1991; 72: 1031-1038), as further evidenced by Boursnell et al. (US 5,719,054), as applied to claims 32, 36, 38, 53 and 54 above, and further in view of Crook et al. (Cell. 1991; 67: 547-556) and Munger et al. (EMBO Journal. 1989; 8: 4099-4105).

Applicant notes that the claims have been amended to require that the sequences are places under the control of independent elements.

In response, the amendment has been fully considered. The discussion above regarding the teachings of Boursnell et al. are incorporated herein.

Claims 44, 46, 48, 55, 56, 62 and 64 rejected under 35 U.S.C. 103(a) as being unpatentable over Lowy et al. (US 5,618,536), Hagensee et al. (Journal of Virology. 1993; 67 (1): 315-322), Borysiewicz et al. (Lancet. June, 1996; 347: 1523-1527), Galloway (Infectious Agents and Disease. 1994; 3: 187-193), and Meyer et al. (Journal of General Virology. 1991; 72: 1031-1038), as further evidenced by Boursnell et al. (US 5,719,054), as applied to claims 32, 36, 38, 53 and 54 above, and further in view of Bubenik et al. (International Journal of Oncology. 1996; 8: 477-481).

Applicant argues that Bubenik et al. does not suggest an MVA vector encoding the papillomavirus polypeptides claimed.

However, the teachings of Bubenik et al. are only required to supply the limitations not addressed previously and provide a motivation to include the limitation with a reasonable expectation of success. The teachings of Bubenik et al. satisfy these criteria.

Bubenik et al. demonstrate that the use of IL-2 as an adjuvant enhances the immunization effect in Syrian hamsters immunized with irradiated HPV 16-transformed tumor cells expressing E6 and E7, see the abstract, the materials and methods section on page 478, Figure 1 on page 479 and the discussion section.

One of ordinary skill in the art at the time the invention was made would have been motivated to incorporate IL-2 of Bubenik et al. into the MVA vaccinia vector of Meyer et al. expressing prophylactic L1 and L2 proteins of Lowy et al. and Galloway, and the therapeutic E6 and E7 proteins of Borysiewicz et al. and Galloway, to augment the immune response to the papillomavirus polypeptides. One of ordinary skill in the art at the time the invention was made would have had a reasonable expectation for expressing IL-2 in the MVA vaccinia vector of

Meyer et al. because Hagensee et al. and Borysiewicz et al. teach expressing papillomavirus polypeptide genes in a vaccinia vector and Meyer et al. use MVA vaccinia virus that allows multiple insertion sites for heterologous inserts. Further, Boursnell et al. teach expressing multiple papillomavirus genes from multiple promoters in the same vaccinia vector. Therefore, one of ordinary skill would have been able to express various papillomavirus polypeptides as well as IL-2 in an MVA vector with a reasonable expectation of success. Therefore, the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made, absent unexpected results.

Applicant notes that the animals administered irradiated cells and IL-2 were protected to a greater extent than animals that had received only irradiated cells. Applicant also notes the immunization protocol of Bubenik et al. requires the administration of twenty injections of IL-2 and that such a quantity of administration is of interest. Applicant states that the injections required by Bubenik et al. would be far more difficult to implement than the gene transfer approach instantly claimed.

Applicant is correct and the examiner agrees that multiple injections of IL-2 would be more cumbersome than administering an expression vector expressing IL-2. Applicant has thankfully identified yet another motivation to express IL-2 in the MVA expression vector of Meyer et al. Regarding the quantity of IL-2 administered by Bubenik et al., it is noted that the instant expression vector claimed includes an independent expression element for IL-2. Once the instant recombinant vector is administered, expression of IL-2 is continuous. Further, since more than one expression vector was administered in the instant working examples, it is concluded that the quantity of IL-2 administered to induce the adjuvanting effect by Bubenik et al. would be

equivalent to the continuous expression of IL-2 within the multiple vectors instantly administered.

Claims 49-51 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lowy et al. (US 5,618,536), Hagensee et al. (Journal of Virology. 1993; 67 (1): 315-322), Borysiewicz et al. (Lancet. June, 1996; 347: 1523-1527), Galloway (Infectious Agents and Disease. 1994; 3: 187-193), Meyer et al. (Journal of General Virology. 1991; 72: 1031-1038), as further evidenced by Boursnell et al. (US 5,719,054), and Bubenik et al. (International Journal of Oncology. 1996; 8: 477-481) as applied to claims 32, 36, 38, 44, 46, 48, 53-56, 62 and 64 above, and further in view of Crook et al. (Cell. 1991; 67: 547-556) and Munger et al. (EMBO Journal. 1989; 8: 4099-4105).

Applicant did not separately address this rejection. This omission is presumed to be inadvertent. The rejection is maintained for reasons of record and as further evidenced by the teachings of Boursnell et al.

Claims 47 and 48 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lowy et al. (US 5,618,536), Hagensee et al. (Journal of Virology. 1993; 67 (1): 315-322), Borysiewicz et al. (Lancet. June, 1996; 347: 1523-1527), Galloway (Infectious Agents and Disease. 1994; 3: 187-193), and Meyer et al. (Journal of General Virology. 1991; 72: 1031-1038), as further evidenced by Boursnell et al. (US 5,719,054), as applied to claims 44, 46, 48, 55, 56, 62 and 64 above, and further in view of Baltz (American Journal of Health-System Pharmacy. 1995; 52: 2574-2585) and Gajewski (The Journal of Immunology. 1996; 156: 465-472).

Applicant argues that Baltz does not teach the instant composition. If the reference anticipated the instant composition, the reference would have been applied under 35 USC 12.

Baltz teaches co-administering an adjuvant, such as B7 molecules, with cancer antigens enhances the immune response to the antigen, see "Adjuvants" on page 2581. These teachings are relevant to the instant invention because papillomavirus antigens are oncogenic and the instant composition requires the administration of a B7 adjuvant. Baltz also reviews vaccine delivery by expressing antigen or cytokine genes into vaccinia virus, see "Recombinant DNA technology" bridging pages 2581-2582.

Applicant argues that the skilled artisan would not have been motivated to incorporate B7.1 into the papillomavirus expressing vector with a reasonable expectation of success because the reference indicates that B7.1 is superior, based on specific excerpts within the reference.

Applicant's arguments have been fully considered, but are found unpersuasive. It is the superiority of B7.1 as a CD8+ stimulator, pointed to by applicant, that would have motivated the ordinary artisan to incorporate B7.1 into the vector of Meyer et al. expressing prophylactic L1 and L2 proteins of Lowy et al. and Galloway, and the therapeutic E6 and E7 proteins of Borysiewicz et al. and Galloway, to augment the immune response to the papillomavirus polypeptides and stimulate the secretion of IL-2. One of ordinary skill in the art at the time the invention was made would have had a reasonable expectation for expressing B7.1 in the MVA vaccinia vector of Meyer et al. because Hagensee et al. and Borysiewicz et al. teach expressing papillomavirus polypeptide genes in a vaccinia vector and Meyer et al. use MVA vaccinia virus that allows multiple insertion sites for heterologous inserts. Further, Boursnell et al. clearly teach expressing more than one heterologous insert from different promoters in a vaccinia vector. One of ordinary skill would further reason to expect success for expressing B7.1 of Gajewski in the MVA vector of Meyer et al. because Baltz teaches cancer vaccine delivery by expressing

antigen or cytokine genes into vaccinia virus vector. Therefore, one of ordinary skill would have been able to express various papillomavirus polypeptides as well as B7.1 in an MVA vector with a reasonable expectation of success. Therefore, the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made, absent unexpected results.

Claims 65, 69, 71, 72, 74, 79 and 80 are rejected under 35 U.S.C. 103(a) as being unpatentable over Borysiewicz et al. (Lancet. June, 1996; 347: 1523-1527), Meyer et al. (Journal of General Virology. 1991; 72: 1031-1038) and Bubenik et al. (International Journal of Oncology. 1996; 8: 477-481), as further evidenced by Boursnell et al. (US 5,719,054).

Claims 75-77 are rejected under 35 U.S.C. 103(a) as being unpatentable over Borysiewicz et al. (Lancet. June, 1996; 347: 1523-1527), Meyer et al. (Journal of General Virology. 1991; 72: 1031-1038) and Bubenik et al. (International Journal of Oncology. 1996; 8: 477-481) as applied to claims 65, 69, 71, 72, 74, 79 and 80 above, and further in view of Crook et al. (Cell. 1991; 67: 547-556) and Munger et al. (EMBO Journal. 1989; 8: 4099-4105), as further evidenced by Boursnell et al. (US 5,719,054).

Applicant argues that Borysiewicz et al. only teaches fused papillomavirus polypeptides.

In response, Boursnell et al. teach un-fused, independently expressed papillomavirus polypeptides from a vaccinia vector.

Applicant also argues that Borysiewicz et al. does not suggest an MVA vector expressing an immunostimulator with E6 and E7 polypeptides.

In reply, Meyer et al. teach the MVA vector, Bubenik et al. teach an immunostimulator, IL-2 and Borysiewicz et al. teach expressing papillomavirus polypeptides in a vaccinia vector and inducing a therapeutic effect.

Therefore, the asserted missing elements discussed by applicant are taught in the references.

One of ordinary skill in the art at the time the invention was made would have been motivated to incorporate IL-2 of Bubenik et al. into the vaccinia vector of Borysiewicz et al. expressing the therapeutic E6 and E7 proteins to augment the immune response to the papillomavirus polypeptides and to control the amounts of IL-2 expressed from the vaccinia vector. One of ordinary skill in the art at the time the invention was made would have had a reasonable expectation for augmenting the immune response to E6 and E7 by expressing IL-2 from the vaccinia vector of Borysiewicz et al. because Bubenik et al. demonstrates an enhanced immune response against E6 and E7 with IL-2 and Boursnell et al. teach un-fused, independently expressed papillomavirus polypeptides from a vaccinia vector.

Neither Borysiewicz et al. nor Bubenik et al. teach the vaccinia virus strain MVA or incorporating the papillomavirus polypeptides into the recited excision regions or the K1L promoter.

Meyer et al. teach six major deletion sites in the wild-type vaccinia Ankara strain attenuate virus pathogenicity to MVA that are not essential to viral replication and, see the abstract and the results section on page 1032-1034. In addition, Meyer et al. teach that the insertion of the K1L gene of the MVA vaccinia strain leads to increased host range and suggests this as a selection system for recombinant viruses expressing foreign genes, see page 1037.

One of ordinary skill in the art at the time the invention was made would have been motivated to incorporate IL-2 of Bubenik et al. into the MVA vaccinia vector of Meyer et al. expressing E6 and E7 proteins of Borysiewicz et al. to augment the immune response to the papillomavirus polypeptides. One of ordinary skill in the art at the time the invention was made would have had a reasonable expectation for expressing IL-2 in the MVA vaccinia vector of Meyer et al. because Borysiewicz et al. teach expressing papillomavirus polypeptide genes in a vaccinia vector, Meyer et al. use MVA vaccinia virus that allows multiple insertion sites for heterologous inserts and Boursnell et al. teach un-fused, independently expressed papillomavirus polypeptides from a vaccinia vector. Therefore, one of ordinary skill would have been able to express various papillomavirus polypeptides as well as IL-2 in an MVA vector with a reasonable expectation of success.

Applicant also asserts that the antitumor effectiveness of Borysiewicz et al. cannot be determined.

The results of Borysiewicz et al. indicate that the cytotoxic immune response elicited by the construct resulted in a therapeutic benefit for one patient, see the results and discussion sections.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO

MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shanon Foley whose telephone number is (571) 272-0898. The examiner can normally be reached on M-F 9:30 AM - 6:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Housel can be reached on (571) 272-0902. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Shanon Foley

JAMES HOUSEL 3/8/04
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600